IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

WYETH LLC, WYETH PHARMACEUTICALS LLC, PF PRISM C.V., PFIZER PHARMACEUTICALS LLC and PFIZER PFE IRELAND PHARMACEUTICALS HOLDING 1 B.V.	)	
Plaintiffs,	)	C.A. No. 16-1305 (RGA) CONSOLIDATED
v.	)	
ALEMBIC PHARMACEUTICALS, LTD., ALEMBIC PHARMACEUTICALS, INC. , SUN PHARMACEUTICAL INDUSTRIES LIMITED and SUN PHARMACEUTICAL INDUSTRIES, INC.,	)	**REDACTED - PUBLIC VERSION**
Defendants.	)	

PLAINTIFFS' *DAUBERT* MOTION TO EXCLUDE CERTAIN EXPERT TESTIMONY BY CRAIG W. LINDSLEY, PH.D.

Plaintiffs Wyeth LLC, Wyeth Pharmaceuticals LLC, PF Prism C.V., Pfizer Pharmaceuticals LLC and Pfizer PFE Ireland Holding 1 B.V. (collectively "Pfizer") submit this motion, pursuant to Local Rule 7.1.2 and Paragraph 10(b) of the Scheduling Order (as amended), for an order excluding trial testimony by defendants' expert Craig W. Lindsley, Ph.D. on the subject of whether Pfizer was diligent in reducing to practice the inventions claimed in U.S. Patent Nos. 7,417,148 ("'148 patent") and 7,919,625 ("'625 patent"), two of the three patents that Pfizer is asserting in this case. The diligence inquiry does not lend itself to the sort of expert opinion testimony that defendants apparently plan to present through Dr. Lindsley. His April 24, 2019 expert report does not make clear how his expertise as a medicinal chemist will assist this Court in understanding the evidence or determining a fact in issue for purposes of

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deciding whether Pfizer was diligent. Testimony by Dr. Lindsley telling the Court what would and would not constitute diligence by the inventors would be improper.[1]

I. BACKGROUND

The '148 patent claims a method of treating or inhibiting the proliferation of chronic myelogenous leukemia ("CML") by providing to a patient in need thereof a therapeutically effective amount of the compound bosutinib, the active ingredient in Pfizer's Bosulif® product. The '625 patent claims a pharmaceutical composition comprising a CML inhibiting amount of bosutinib. Both patents claim priority to provisional application No. 60/517,819, filed on November 6, 2003.

In challenging the validity of the '148 and '625 patents, defendants rely, *inter alia*, on art published during the period November 2002-January 2003, *i.e.*, less than one year before the November 6, 2003 priority date. Those references qualify as prior art under the applicable version of 35 U.S.C. § 102(a) only if they pre-dated the patentee's invention.

At trial, Pfizer expects to demonstrate through the testimony of individuals who worked on the bosutinib development project that (1) the inventors conceived the inventions claimed in the '148 and '625 patents prior to the publication of the art that defendants rely on under § 102(a); and (ii) beginning before the publication of that art and continuing until constructive reduction to practice of the inventions of the '148 and '625 patents on November 6, 2003, Pfizer diligently worked towards reduction to practice of its claimed inventions. The effort conducted by Pfizer during the period in question included synthetic chemistry and process development, formulation development and toxicology testing. Evidently, based on his experience as a research scientist at three pharmaceutical companies, Dr. Lindsley plans to testify that he has

[1] Pfizer will not be calling an expert witness at trial to opine on the issue of diligent reduction to practice.

concluded that Pfizer's work on bosutinib during the time in question did not in his view qualify as diligence.[2]

II. ARGUMENT

Motions to preclude evidence are committed to the discretion of the Court which serves as a gatekeeper to ensure that evidence is relevant and reliable. See *Pineda v. Ford Motor Co.*, 520 F.3d 237, 243 (3d Cir. 2008). Whether expert testimony is admissible is a question of law governed by Fed. R. Evid. 702. *See Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579, 589-90 (1993). Expert testimony is admissible under Rule 702 only if the expert's "scientific, technical or other specialized knowledge will help the trier of fact to understand the evidence or to determine a fact in issue." Fed. R. Evid. 702(a).

According to the Federal Circuit:

> The diligence requirement implements the principle that, to antedate a reference, the applicant must not only have conceived the invention before the reference date, but must have reasonably continued activity to reduce the invention to practice.

ATI Tech. ULC v. Iancu, 920 F.3d 1362, 1369 (Fed. Cir. 2019). The court explained that the "principles underlying the law of diligence have long been recognized":

> No general standard, by which diligence can be estimated, has been established by the law, nor, in the nature of things, is such a standard possible. It must be reasonable, under all the circumstances of the particular case in question. The character of the invention; the health, the means, the liberty of the inventor; his occupation upon kindred or subordinate inventions, – are proper subjects for consideration. Such reasonable diligence does not involve uninterrupted effort nor the concentration of his entire energies upon this such enterprise.

[2] Pfizer is not challenging on *Daubert* grounds testimony by Dr. Lindsley on § 112 issues.

Id. at 1374. "Whether a patent antedates a reference is a question of law based on subsidiary findings of fact." *Perfect Surgical Techniques, Inc. v. Olympus Am., Inc.*, 841 F.3d 1004, 1008 (Fed. Cir. 2016).

Here, in opposing Pfizer's effort to establish an invention date earlier than the late 2002 and early 2003 art that defendants are relying on, defendants plan to offer the testimony of Dr. Lindsley, who received a Ph.D. in chemistry from the University of California, Santa Barbara, in 1996, and has been a professor of pharmacology at Vanderbilt University since 2010. (Lindsley CV, Exhibit A hereto). Previously, Dr. Lindsley worked as a medicinal chemist at Merck Research Laboratories, Eli Lilly & Co. and Parke-Davis Pharmaceuticals. (*Id*.) Dr. Lindsley's expert report states that based on his time at those companies, he "understand[s] how timing and execution of invention disclosures and patent filings are handled in the pharmaceutical industry." (Lindsley Opening Rep., Ex. B hereto at ¶¶ 8-11). Dr. Lindsley asserts that having purportedly "reviewed the evidence that Plaintiffs cite in support of their assertion of diligence," he is prepared to opine "that the named inventors did not diligently work to reduce the invention to practice between either November 16, 2002, and November 6, 2003 or January 15, 2003 and November 6, 2003." (Lindsley Opening Rep., Ex. B at ¶¶ 76-82).

In accordance with *Daubert*, the Court should bar Dr. Lindsley's testimony on the diligence issue because his assessment of the facts, his discussion of industry timelines and his conclusory determination that there was a lack of diligence on Pfizer's part will not "help the trier of fact to understand the evidence or to determine a fact in issue." Fed. R. Evid. 702(a). The Court is to make the diligence determination here based on the factual record and the applicable standard articulated by the case law. Dr. Lindsley sheds no light on what would make him – or anyone for that matter – a "diligence" expert and he does not explain how his personal

evaluation of Pfizer's effort would be of any relevance to the Court. Not surprisingly, at his deposition, Dr. Lindsley acknowledged that he has not studied, taught or published on diligence in reduction to practice. (Lindsley Dep. Tr., Ex. C hereto at 86-87).

In sum, this Court is fully capable of hearing the testimony of those who participated in developing bosutinib, reviewing the underlying documents and determining whether Pfizer engaged in "reasonably continuous diligence," *Perfect Surgical Techniques*, 841 F.3d at 1009, during the period in question. Opinion testimony by Dr. Lindsley regarding how the Court should decide the issue would be improper.

III. CONCLUSION

Based on the foregoing, Plaintiffs respectfully request that the Court preclude Dr. Lindsley from providing expert opinion testimony on the issue of diligence in reduction to practice.

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/s/ Megan E. Dellinger

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Attorneys for Plaintiffs

August 30, 2019

RULE 7.1.1 CERTIFICATE

Pursuant to D. Del. LR 7.1.1, I hereby certify that the subject of the foregoing motion has been discussed with counsel for Defendants and that the parties have been unable to reach agreement.

/s/ Megan E. Dellinger
Megan E. Dellinger (#5739)

EXHIBIT A

Dr. Craig W. Lindsley

Home Address:
[redacted]

Laboratory Address:
Department of Pharmacology
MRBIV (Langford), 12415D
Vanderbilt Medical Center
Nashville, TN 37232-6600

E-mail: craig.lindsley@vanderbilt.edu; phone (office): 615-322-8700
Web site: www.lindsleylab.com
Citizenship: US
Marital status: [redacted]

Education:

1997 – 1999	Postdoctoral Fellow, Harvard University, Cambridge, MA
1992 - 1996	Ph.D., University of California, Santa Barbara, Santa Barbara, CA
1988 - 1992	B.S., Chemistry, California State University, Chico, Chico, CA

Academic Appointments and Research Experience:

01/2011-present	**Professor of Pharmacology (*with tenure*), Professor of Chemistry; Co-Director, Vanderbilt Center for Neuroscience Drug Discovery; Director of Medicinal Chemistry, Vanderbilt Center for Neuroscience Drug Discovery (formerly Vanderbilt Program in Drug Discovery); Director of Drug Discovery, Human Chemical Sciences Institute (Scripps-Vanderbilt); PI, Vanderbilt MLPCN Specialized Chemistry Center; Editor-in-Chief, *ACS Chemical Neuroscience*** *Member, Vanderbilt Institute of Chemical Biology* Vanderbilt University School of Medicine, Vanderbilt University (*Medicinal Chemistry, Drug Discovery, Total Synthesis, Chemical Biology*)
04/2010-present	**Professor of Pharmacology (*with tenure*), Professor of Chemistry; Director of Medicinal Chemistry, Vanderbilt Program in Drug Discovery; PI, Vanderbilt MLPCN Specialized Chemistry Center; Editor-in-Chief, *ACS Chemical Neuroscience*** *Member, Vanderbilt Institute of Chemical Biology* Vanderbilt University School of Medicine, Vanderbilt University (*Medicinal Chemistry, Drug Discovery, Total Synthesis, Chemical Biology*)
05/08-04/2010	**Associate Professor of Pharmacology (*with tenure*), Associate Professor of Chemistry; Director of Medicinal Chemistry, Vanderbilt Program in Drug Discovery; PI, Vanderbilt MLPCN Specialized Chemistry Center; Co-Director, VICB Synthesis Facility, Editor-in-Chief, *ACS Chemical Neuroscience*** *Member, Vanderbilt Institute of Chemical Biology* Vanderbilt University School of Medicine, Vanderbilt University (*Medicinal Chemistry, Drug Discovery, Total Synthesis, Chemical Biology*)
09/06 – 05/08	**Associate Professor of Pharmacology, Associate Professor of Chemistry;**

Director of Medicinal Chemistry, Vanderbilt Program in Drug Discovery;
Director, Vanderbilt MLSCN Chemistry Molecular Probe Center;
Co-Director, VICB Synthesis Facility
Member, Vanderbilt Institute of Chemical Biology
Vanderbilt University School of Medicine, Vanderbilt University
(*Medicinal Chemistry, Drug Discovery, Total Synthesis, Chemical Biology*)

07/05-09/06 **Senior Research Fellow/Group Leader**
(Medicinal Chemistry Department)
Merck Research Laboratories, Merck & Co., West Point, PA
Supervise a group of 19 Ph.D. and B.S./M.S. scientists
(Neuroscience, Antiviral, Cardiovascular, Cancer, Small Molecule PPIs)

08/02-07/05 **Research Fellow/Group Leader**
(Medicinal Chemistry Department)
Merck Research Laboratories, Merck & Co., West Point, PA
(Cancer, Neuroscience,Antiviral)

06/01-08/02 **Senior Research Chemist/Group Leader**
(Medicinal Chemistry Department)
Merck Research Laboratories, Merck & Co., West Point, PA
(Cancer, Neuroscience, Antiviral)

05/00-6/01 **Senior Organic Chemist (Chemistry Research Technologies)**
Eli Lilly & Co., Indianapolis, IN
Lead Discovery (H3 antagonists, MC4 agonists)

04/99-05/00 **Senior Scientist (Medicinal Chemistry)**
Parke-Davis Pharmaceuticals, Ann Arbor, MI
Anti-Viral (HIV), Anti-Bacterial, SERM and Rasta resin research.

05/97-04/99 **Postdoctoral Research with Professor Matthew D. Shair**
Harvard Institute of Chemistry and Cell Biology (ICCB)/Department of Chemistry & Chemical Biology; Harvard University, Cambridge, MA
Biomimetic Solid Phase Synthesis of Benzoxanthenone Unnatural Products Novel Organometallic and Solid Phase Methodologies.

06/92-11/96 **Graduate Research with Professor Bruce Lipshutz,**
University of California, Santa Barbara, Santa Barbara, CA
Organometallic Methodology, Novel Bi-Directional Polyene Linchpins for All-E Polyene Synthesis, Development of New Protecting Groups.

06/91-05/92 **Undergraduate Research with Professor David Ball,**
California State University, Chico, Chico, CA
Progress Towards the Total Synthesis of Borrellidin.

Summer 1991 **NSF Summer Undergraduate Research Fellowship with Professor Phillip Cruz**
University of California, Santa Cruz, Santa Cruz, CA

Isolation, Purification and Characterization of Secondary Sponge Metabolites.

Teaching Experience

Fall 2006 – present	**Professor of Pharmacology & Chemistry** Vanderbilt University Medical Center/Vanderbilt University Pharm 327 *Modern Drug Discovery* Chem 324 *Heterocyclic Chemistry* IGP 300B: *Small Molecule Design for Biologists*
Fall 2004	**Adjunct Faculty** Villanova University Chem 398 *Graduate Course on Medicinal/Combinatorial Chemistry*
2000-2001	**Part-time Instructor/Lecturer** Indiana University/Purdue University at Indianapolis (IUPUI) *General and Organic Chemistry lectures and laboratory*
1992-1996	**Graduate Teaching Assistant** University of California, Santa Barbara *Organic Laboratory, Honors Organic lab, NMR lab*

Professional Organizations:

- American Chemical Society (1991-present)
- American Society of Pharmacology and Experimental Therapeutics (2009-present)

Professional Activities:

Intramural:

Thesis Committees:

J. Phillip Kennedy	Chemistry	2007-2010, Chair
R. Nathan Daniels	Chemistry	2007-2010, Chair
Sameer Sharma	Chemical & Physical Biology	2007-2009, Member
Leslie Aldrich	Chemistry	2008-present, Chair
Olgubeminiyi Fadeyi	Chemistry	2008-present, Chair
Michael Schulte	Chemistry	2009-present, Chair
Gordon Lemmon	Chemical & Physical Biology	2008-present, Chair
Paige Selvey	Pharmacology	2007-present, Chair
Sydney Stoops	Pharmacology	2008-present, Member
Nicole Miller	Pharmacology	2008-2010, Member
Jonathan Hemphill	Chemistry	2008-present, Member
Sean Deguire	Chemistry	2008-present, Member
Evan Lebois	Pharmacology	2008-2010, Member
Thomas Bridges	Pharmacology	2007-2010, Member
Steve Townsend	Chemistry	2007-present, Member
Robert Lavieri	Pharmacology	2007-present, Member
Uyen Le	Chemical & Physical Biology	2009-present, Member
John Brogan	Chemical & Physical Biology	2009-present, Member
Matthew O'Reilly	Chemistry	2010-present, Chair
Kris Hahn	Chemistry	2010-present, Chair

Tim Senter	Chemistry	2010-present, Chair
Josh Bruner	Chemistry	2011-present, Chair

Extramural:

NIH, grant reviewer and/or ad hoc on 8 NIH panels including Synthetic Chemistry and Biology A. Standing member of NIH Drug Discovery Review Panel.

Reviewer for: *Organic Letters, Journal of Organic Chemistry, Journal of Medicinal Chemistry, Journal of the American Chemical Society, Bioorganic and Medicinal Chemistry Letters* and *Current Topics in Medicinal Chemistry*

Medicinal Chemistry Consultant for: Amgen, Abbott, Eisai, Michael J Fox Foundation

Co-Chair, Chemistry Coordination Committee, MLPCN (2007-present)

Editorial Positions:

- Editor-in-Chief, *ACS Chemical Neuroscience* – 2009-onward
- Associate Editor, *Current Topics in Medicinal Chemistry* – 2007-2009.
- Editorial Advisory Boards: *Journal of Combinatorial Chemistry, Current Topics in Medicinal Chemistry, International Journal of High-Throughput Screening, International Journal of Drug Design & Discovery.*
- Guest Editor, *Curr. Top. Med. Chem*., issue on Small Molecule Protein-Protein Inhibitors (2006/2007)
- Guest Editor, *Curr. Top. Med. Chem*., issue on Metabotropic Glutamate Receptors (2004/2005)

Review Positions, Advisory Boards and Honors:

- Vanderbilt Leadership of a Multi-Investigator Team Award for Two or More Faculty Working Collaboratively or in a Multidisciplinary Manner to Address Important Biological Processes and/or Diseases, 2011.
- 'Most Cited Article 2003-2010' *Bioorg. Med. Chem. Lett.* (ref. 26)
- Top 50 'Most Cited Articles 2003-2010' *Bioorg. Med. Chem. Lett.* (ref. 40)
- Invited Instructor, Drew University Medicinal Chemistry Short Course, 2010-onward
- ASPET-Astellas Award for Translational Pharmacology, 2010
- Organizer, Keystone Symposia on 'Early Stage Drug Discovery', 2011.
- Faculty of 1000 Biology
- Thomson Reuters *Essential Science Indicators*^{SM} Hot New Paper, Most Cited in Field of Pharmacology 2008/2009 (Review ref. 28)
- 6th Most Accessed and Downloaded Manuscript in 2009, *ChemMedChem* (ref. 70)
- Co-Chair, Allosteric Modulator Session (MEDI), ACS 238th National Meeting 2009.
- Most Read and Cited Article 2008, *Journal of Combinatorial Chemistry* (Review ref. 23)
- Most Read and Cited Article 2008, *ACS Chemical Biology* (Review ref. 27)
- Abbott - medicinal chemistry consultant, 2010-onward

- Eisai - medicinal chemistry consultant, 2008-onward
- Amgen – medicinal chemistry consultant, 2007-onward
- Reuter's – medicinal chemistry consultant, 2007-onward
- Most Cited Paper 2005-2008 Award, *Bioorg. Med. Chem. Lett.* (reference 27).
- Assessor – Michael J. Fox Foundation for Parkinson's Research, 2006-onward
- Scientific Advisory Board Member. NIH Chemical Genomics Center, 2004-onward
- NIH SEP Pilot Library Grant Review Committee – 2005-2007
- Innovator/key contributer to six MERCK preclinical candidates: **MK-7816** (insomnia), **MK-2637** (schizophrenia), **MK-1832** (atrial fibrillation), **MK-6673** (oncology), **MK-2206** (oncology) and [^{18}F]**MK-6577** (schizophrenia tracer).
- Early Development Team (EDT) Chemistry Representative MK-2637
- Merck Research Labs (MRL) Chemistry Representative: Schizophrenia and Neuroscience Target Area Group (TAGs)
- Most Cited Paper 2003-2006 Award, *Bioorg. Med. Chem. Lett.* (reference 26).
- 3rd most downloaded and 2nd most cited manuscript in 2005, *Bioorg. Med.Chem.Lett.* (reference 26)
- Top 25 most downloaded manuscripts in 2005, *Bioorg. Med.Chem.Lett.* (reference 27)
- Merck Research Labs (MRL) Quarterly Stock Grant Award: 1Q2005, 4Q2005, 1Q2006 (2)
- LHS Alumni Hall of Honor Inductee, 2005
- TES lead optimization paradigm featured in Genetic Engineering News, Vol. 25(14), 2005
- Aldrich commercialized our Rasta resins utilizing our MAOS protocol – 2005
- Our MAOS research featured in C&E NEWS, Vol. 82 (50), Exclusive Online – 2004
- Advisory Board Member. World Pharmaceutical Congress - 'Hit-to-Lead: Streamlining Lead Generation to Enhance Downstream Success' Conference, 2004
- Merck Award for Excellence, Merck Research Laboratories, 2002, 2005, 2006 (3)
- 'Change the World' Award, Eli Lilly & Co., 2001
- Parke-Davis/University of Michigan Mentor/Instructor, 1999-2000
- Harvard Institute of Chemistry and Cell Biology Postdoctoral Fellowship Recipient, 1997-1999
- Robert H. DeWolfe Award for Excellence in Undergraduate Instruction, UCSB, 1995-1996
- Outstanding Graduating Senior in Chemistry, CSUC, 1992
- American Institute of Chemists Award for Outstanding Senior in Chemistry, CSUC, 1992
- President, Student Affiliates of the American Chemical Society, CSUC chapter, 1991-1992
- NSF Summer Undergraduate Research Fellowship Recipient, 1991

STUDENTS SUPERVISED:

Over 20 rotation students (Pharmacology, Chemistry and CPB)

J. Phillip Kennedy - Chemistry Graduate Student (2006-2010); currently postdoc in Fesik lab
R. Nathan Daniels - Chemistry Graduate Student (2006-2010); currently postdoc in Fesik lab
Olgubeminiyi Fadeyi - Chemistry Graduate Student

Dr. Craig W. Lindsley
Michael Schulte - Chemistry Graduate Student
Leslie Aldrich - Chemistry Graduate Student
Syndey Stoops - Pharmacology Graduate Student
Thomas Bridges - Pharmacology Graduate Student (2006-2010); currently postdoc in Daniels lab
Evan Lebois - Pharmacology Graduate Student (2008-2010); currently in Emory Ph.D. program
Robert Lavieri - Pharmacology Graduate Student
Sameer Sharma – CPB Graduate Student (2007-2009); currently in VU MBA Program
Uyen Le – Chemical and Physical Biology Graduate Student
John Brogan - Chemical and Physical Biology Graduate Student
Patirck Gentry - Chemical and Physical Biology Graduate Student
Tim Senter - Chemistry Graduate Student
Kris Hahn - Chemistry Graduate Student

Supervised over 12 Vanderbilt Chemistry Undergraduate Researchers

POSTDOCTORAL FELLOWS SUPERVISED:
Jana Lewis (2007-2009); currently Sr. Scientist at Living Proof, Inc.
Jason Buck (2007-2008); currently postdoc in VU Imaging Center
Ya Zhou (2007-2009); currently staff scientist in VCNDD
Dustin Haddenham (2010- 2011); currently, Scientists at Boehringer-Ingelheim (Process Chemistry)
Chris Tarr (2010-)
Steven Townsend (2010-)
Margie Mattmann (2011-)

VPDD/MLPCN STAFF SCIENTISTS SUPERVISED: 10 Ph.D.s, 18 B.S./M.S.

MERCK: Supervised a group of 20 Medicinal Chemists (4 Ph.D.s, 16 B.S./M.S.)

Funding (Grants):

Active

- VU Therapeutic Discovery Grant 'mGluR4 PAMs for Parkinson's Disease' ($4.5 million), co-PI, 01/01/2007-02/28/2010, 0% effort.
- Michael J. Fox Foundation LEAPS Award 'mGluR4 PAMs for PD' ($4.4 million), co-PI, 01/01/2008 -12/31/2011, 10% effort.
- 1RO1MH082867-01 'Sel. M1 mAChR Allost. Mod. for Schizophrenia' ($1.12 million), PI, 05/20/2008-04/30/2013, 18% effort.
- 1RO1DA023947-01 'Partial Antag. of mGluR5 for the Treatment of Cocaine Addiction ($1.36 million), PI, 06/01/2008-05/31/2013, 20% effort.
- 1U54MH084659-01 'Vanderbilt Spec. Chem. Center for Accel. Probe Dev.' ($25.9 million), PI, 09/01/2008-05/31/2014, 25% effort.
- 1U01MH087965-01 'Vanderbilt NCDDDG for Discovery of Novel Treatments for Schizophrenia' ($11.3 million), co-PI, 12/01/2009-11/30/2014, 15% effort.
- 1U54MH084659-S01 'Design and synthesis of libraries of small molecule protein-protein inhibitors' ($1 million), PI, 06/01/2010 – 05/31/2012, no effort.
- 1U54MH084659-S02 'DMPK Profiling and Optimization of MLPCN Probes'($1 million), PI, 06/01/2010 – 05/31/2012, no effort.
- McDonnell Foundation, VUMC220020246 'PLD Inhibitors for the Treatment of Cancer'($150K), co-PI, 08/01/2010 – 07/31/2011, no effort.

Funding (Corporate Partnerships):

- VUMC33842, Seaside Therapeutics 'mGluR5 Partial Antagonists for the Treatment of FXS' ($4.5 million), co-PI, 12/01/2007-6/31/2011, 1% effort.
- VUMC34998, Johnson & Johnson 'mGluR5 Positive Allosteric Modulators for Schizophrenia' ($11 million), co-PI, 12/01/2008-12/31/2011, 1% effort.

- VUMC36176, Seaside Therapeutics 'M1 Antagonists for the Treatment of FXS' ($5.0 million), co-PI, 01/01/2010-12/31/2012, 1% effort.

Completed

- Alzheimer Association IIRG-07-57131 'Novel Muscarinic Therapeutics for AD' ($239 K), PI.
- VICB Pilot Project Grant 'M1 PAMs for Alzheimer's Disease' ($45K), PI
- VICB Pilot Project Grant 'GLP-1 PAMs for Diabetes' ($45K), co-PI
- ACS-IRG 'Allosteric Akt and PDK1 inhibitors' ($20K), PI
- 3U54 MH074427-02S1, NIH/MLSCN Chemistry Core Supplement ($500K), PI
- Vanderbilt UCDPG Infrastructure Grant 'Preparative Chiral HPLC' ($174,600), co-PI

Bilbiometrics (based on Web of Knowledge Database)

- Total citations (1994-2010): 2,874
- Average citations per manuscript: 15.3; Average citations per year: 159.7
- h-index: 29

Publications:

In Preparation

14. Noetzel, M.J.; Rook, J.M.; Vinson, P.N.; Cho, K.P.; Days, E.; Zhou, Y.; Rodriguez, A.L.; Lavreysen, H.; Stauffer, S.R.; Niswender, C.M.; Xiang, Z.; Daniels, J.S.; Lindsley, C.W.; Weaver, C.D.; Conn, P.J. 'Positive allosteric modulators of the metabotropic glutamate receptor subtype 5 have in vivo activity independent of their pharmacological classification' *Mol. Pharm., in preparation.*

13. Digby, G.J.; Walker, A.G.; LeBois, E.P.; Utley, T.J.; Xiang, Z.; Miller, N.R.; Plumley, H.C.; Davis, A.A.; Morrison, R.; Daniels, S.; Lindsley, C.W.; Conn, P.J. 'Discovery and characterization of VU0364572, A CNS-penetrant M1-selectiver partial agonist that increases activity in medium spiny neurons and hippocampus' *Nat. Chem. Bio., in preparation.*

12. Selvy, P.E.; Lindsley, C.W.; Bornhop, D.A.; Brown, H.A. 'Novel bimodal mechanism of small molecule inhibition of lipid signaling' *Nature, in preparation*.

11. O'Reilly, M.C.; Lindsley, C.W. 'Enantioselective synthesis of protected morpholines' *Org. Lett., in preparation*

10. Schulte, M.L.; Fadeyi, O.O.; Lindsley, C.W. 'Highly diasteroselective and general synthesis of primary β-fluoroamines' *Org. Lett., in preparation.*

9. Selvy, P.E.; Lavieri, R.; Lindsley, C.W.; Brown, H.A. 'Phospholipase D: enzymology, signaling, and chemical modulation. *Chem. Rev., in preparation (invited).*

8. Schulte, M.L.; Lindsley, C.W. 'Tropane-based alkloaids as muscarinic antagonists for the treatment of asthma, obstructive pulmonary disease and motion sickness' in *Bioactive Heterocyclic Compound Classes: Pharmaceuticals and Agrochemicals*, Dinges, J., Ed., Wiley-VCH Verlag GmbH & Co., Germany, *in preparation*.

7. Lindsley, C.W. and Conn, P.J. 'Allosteric Modulation of GPCRs' *J. Med. Chem., in preparation*

6. Gentry, P.W.; Salovich, J.; Engers, D.; Gogliotti, R.; Cheung, Y-Y.; Lindsley, C.W.; Hopkins, C.R. 'One-step microwave-assisted synthesis of substituted hydantoins from amino acids and isocyanates' *Tetrahedron Lett., in preparation.*

5. Williams, D.L. Jr; Wolkenberg, S.E.; Zhao, Z.; Wisnoski, D.D.; Leister, W.H.; O'Brien, J.A.; Lemaire, W.; Jacobson, M.A.; Kinney, G.G; Pettibone, D.J.; Tiller, P.R.; Smith, S.; Gibson, C.; Ma, B.K.; Polsky-Fisher, S.L.; Lindsley, C.W.; Hartman, G.D; Sur, C. '*In vitro* and *in vivo* pharmacology of 2,4-dichloro-*N*-((1-propylsulfonyl)-4-(pyridine-2-yl)piperidin-4-yl)methyl) benzamide, a potent and orally active GlyT1 inhibitor' *J. Pharmacol. Exp. Therapeut., in preparation.*

3. Brogan, J.T.; Lindsley, C.W. 'Total synthesis of (+)-tryparginine and (+)-5-bromo-tryparginine via Bronsted base catalysis' *Org. Lett., in preparation.*

3. Fadeyi, O.; Lindsley, C.W. 'Novel Methodology for the Enantioselective Synthesis of Decahydropyrrol[1,2-*a*]azocines, Octahydropyrrolo[1,2-*a*]azepines and Octahydroindolizines' *J. Am. Chem. Soc., in preparation.*

2. Kane, A.S.; Williams, R.; Lindsley, C.W.; Conn, P.J.; Jones, C.K. 'Glycine transporter 1 inhibitor ACPPB facilitates extinction of conditioned fear responses in preclinical model of PTSD' *Proc. Natl. Acad. Sci. USA, in preparation.*

1. Kane, A.S.; Bubser, M.; Bridges, T.M.; Kennedy, J.P.; Deutch, A.Y.; Lindsley, C.W.; Conn, P.J.; Jones C.K. 'Modulation of monoamine turnover and antipsychotic-like activity in rats using novel selective allosteric activator of the M_4 muscarinic acetylcholine receptor' *J. Neurosci., in preparation*.

In Press/submitted

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48. Bridges, T.; Brady, A.; Shirey, J.; Marlo, J.; Jones, C.K.; Conn, P.J.; **Lindsley, C.W.** 'Sub-type selective allosteric modualtion of the M1 and M4 muscarinic receptors: novel agonists and potentiatiors relevant to Alzheimer's disease and schizophrenia' ACS-EFMC Frontiers in CNS and Oncology Medicinal Chemistry, Sienna, Italy, October 7-9, 2007 (voted best poster).

47. **Lindsley, C.W.** 'Natural Product Guided Synthesis: Total Synthesis, Molecular Editing and Biological Evaluation of Natural Products' ICCA X, Nashville, TN, August 12-15, 2007 (invited speaker).

46. Williams, R.; Jones, C.; Brady, A.; Conn, P.J.; **Lindsley, C.W.** 'Development of M1 muscarinic modulators' Gordon Research Conference on Combinatorial Chemistry, New London, NH, June 3-7, 2007.

45. **Lindsley, C.W.** 'Preclinical Drug Discovery in an Academic Setting - It is Possible' Gordon Research Conference on Combinatorial Chemistry, New London, NH, June 3-7, 2007 (invited speaker).

44. Zhao, Z.; Nolt, M.B.; McDonald, T.P.; Maxwell. J.W.; Kinose, F.; Thut, C.; **Lindsley, C.W.**; Wolkenberg, S.E. 'Discovery of selective agonists of somatostatin receptor subtype 2 (SSTR2): application of an iterative analogue library approach' ACS MARM 2007, Ursinus College, Collegeville, PA May 16, 2007.

43. **Lindsley, C.W.** 'Development of novel, centrally active GlyT1 inhibitors that further validate the NMDA hypofunction hypothesis of schizophrenia in preclinical animal models' International Congress on Schizophrenia Research (ICOSR), Colorado Springs, CO, March 28-May1, 2007.

42. **Lindsley, C.W.** 'Progress towards validation of the NMDA hypofunction hypothesis of schizophrenia: discovery and development of centrally active glycine transporter (GlyT1) inhibitors' American College of Neuropsychopharmacology 45th Annual Meeting, Hollywood, FL, December 3-7, 2006.

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40. Wolkenberg, S.E.; Zhao, Z.; Nolt, B.M.; Wisnoski, D.D.; Nanda, K.; Trotter, B.W.; Leister, W.H.; Hartman, G.D.; **Lindsley, C.W.** 'Application of an iterative analogue library approach to cardiovascular and neuroscience programs' Gordon Research Conference on Combinatorial Chemistry, Oxford, UK, August 20-25, 2006. (Voted Best Poster)

39. **Lindsley, C.W.** 'Discovery and development of the first centrally active mGluR5 positive allosteric modulators' Gordon Research Conference on Medicinal Chemistry, New London, NH, August 6-11, 2006 (invited speaker).

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36. Jesudason, C.D.; Beavers, L.S.; Cramer, J.W.; Dill, J.; Finley, D.R.; Gleason, S.D.; Hemrick-Leuke, S.K.; **Lindsley, C.W.**; Nelson, D.L.G.; Stevens, F.C.; Gadski, R.A.; Oldham, S.W.; Pickard, R.T.; Siedem, C.S.; Sindelar, D.K.; Singh, A.; Watson, B.M.; Witkin, J.M.;Hipskind, P.A. '(3-Piperidin-1-yl-propoxy)-tetrahydroisoquinolines and tetrahydrozaepines: A novel series of selective H3 antagonists' 35th European Histamine Research Society Meeting, Delphi, Greece, May 10-13, 2006.

35. Wang, Y.; McClain, R.T.; Dudkina, A.; Cox, A.L.; Denicola, C.J.; **Lindsley, C.W.** 'Automated purification and post purification support in a high throughput synthesis group' Prep 19th International Symposium, Baltimore, Maryland, May 14-17, 2006.

34. McClain, R.T.; Varga, S.L.; Wolkenberg, S.E.; **Lindsley, C.W.**; Smiley, M.A.; Nolt, M.B. 'Convenient preparation of substituted 5-amino oxazoles via a microwave-assisted Cornforth rearrangement' Cambridge Health Institute: Chemistry Enabled Drug Design Meeting, San Diego, CA April 23-26, 2006.

33. Yang, F.V.; Shipe, W.D.; **Lindsley, C.W.** 'General microwave-assisted protocol for the expedient synthesis of quinoxalinones' Microwaves In Chemistry 4th International Conference, Orlando, FL. March 10, 2006.

32. Wisnoski, D.D.; **Lindsley, C.W.**; Williams Jr., D.L.; Sur, C. 'Discovery and development of the first centrally active mGluR5 positive allosteric modulators' Gordon Research Conference on Combinatorial Chemistry, Andover, NH, August 21-26, 2005 (invited poster).

31. **Lindsley, C.W.** 'Lead optimization driven by iterative analogue library synthesis: development of of novel allosteric Akt kinase inhibitors' Gordon Research Conference on Combinatorial Chemistry, Andover, NH, August 21-26, 2005 (invited speaker).

30. **Lindsley, C.W.** 'Hit-to-Lead-to-Proof of Concept: Akt kinase inhibitors and mGluR5 positive allosteric modulators' World Pharmaceutical Congress - Hit-to-Lead: Streamling Lead Generation to Enhance Downstream Success, Philadelphia, PA May 24-25, 2005 (invited speaker).

29. **Lindsley, C.W.** 'Discovery and development of the first centrally active mGluR5 positive allosteric modulators' ACS Mid-Atlantic Regional Meeting, Rutgers University, New Brunswick, NJ, May 23, 2005 (invited speaker).

28. **Lindsley, C.W.** 'Technology Enabled Synthesis: A new paradigm for lead optimization' ACS ProSpectives on Medicnal Chemistry, Boston, MA, May 15-18, 2005 (invited speaker).

27. Zhao, Z.; Leister, W.H.; Wisnoski, D.D.; Wang, Y.; Wolkenebrg, S.E.; **Lindsley, C.W.** 'Microwave-assited organic synthesisof quinoxalines and 5,6-diphenylpyrazin-2(1H)-one libraries as isoyzme selective Akt inhibitors' ACS ProSpectives on Medicnal Chemistry, Boston, MA, May 15-18, 2005.

26. **Lindsley, C.W.** 'Technology enhanced medicinal chemistry: development of allosteric Akt

kinase inhibitors' The Royal Society of Chemistry – High Throughput Medicinal Chemistry, London, UK, May 10, 2005 (invited speaker).

25. **Lindsley, C.W.** 'Technology Enabled Synthesis: application to the development of the first centrally active mGluR5 positive allosteric modulators' Vanderbilt Institute of Chemical Biology Nashville, TN, February 9, 2005 (invited speaker).

24. Huber, H.E.; Barnett, S.F.; Defeo-Jones, D.; Hancock, P.J.; Haskell, K.M.; Jones, R.E.; Leander, K.R.; **Lindsley, C.W.**; Robinson, R.G.; Zhao, Z.J. 'Akt inhibitors as chemosensitizers' Nature Biotechnology 2005 Winter Symposium, Miami, FL, February 5-9, 2005.

23. **Lindsley, C.W.** 'Application of microwave-assisted organic synthesis (MAOS) for lead optimization' LabAutomation 2005, San Jose, CA, February 3, 2005 (invited speaker).

22. Wang, Y.; Leister, W.; McClain, R.; Dudkina, A.; Wolkenberg, S.W.; **Lindsley, C.W.** 'Automated post-purification sample handling in a high-throughput medicnal chemistry group' LabAutomation 2005, San Jose, CA, February 3, 2005.

21. Zhao, Z.; Wisnoski, D.D.; Leister, W.H.; Wang, Y.; Wolkenberg, S.E.; **Lindsley, C.W.** 'Microwave-assisted organic synthesis of quinoxaline and 5,6-diphenylpyrazin-2(1*H*)-one libraries as Akt inhibitors' Microwave User Group Meeting, Princeton, New Jersey, October 26, 2004.

20. Balitza, A.E.; Barnett, S.F.; Bilodeau, M.T.; Defeo-Jones, D.; Hartman, G.D.; Hoffman, J.M.; Huber, H.E. Jones, R.E.; Kral, A.M.; **Lindsley, C.W.**; Manley, P.J.; Robinson, R.G.; Smith, A.M.'Development of diaryl-naphthyridine inhibitors of Akt kinase' American Chemical Society 228th National Meeting, Philadelphia, Pennsylvania, August 22-28, 2004.

19. **Lindsley, C.W.** 'Establishing an effective lead discovery and development operation' The National Institute of Health, Bethesda, MD., August 27, 2004 (invited speaker).

18. Defeo-Jones, D.; Barnett, S.F.; Hancock, P.J.; Haskell, K.M.; Leander, K.R.; Fu, S.; Robinson, R.G.; Huber, H.E.; Jones, R.E.; Zhao, Z.; Duggan, M.E.; **Lindsley, C.W.** 'Tumor cell sensitization to apoptotic stimuli by selective inhibition of specific Akt/PKB family members'Gordon Research Conference on Cancer Models and Mechanisms, Salve Regina University, New Port, RI, August 1-6, 2004.

17. **Lindsley, C.W.** 'Development pleckstrin homology domain dependent and isozyme selective Akt kinase inhibitors' Gordon Research Conference on Medicinal Chemistry, New London, NH, August 1-6, 2004 (invited speaker).

16. Defeo-Jones, D.; Barnett, S.F.; Hancock, P.J.; Haskell, K.M.; Leander, K.R.; Fu, S.; Robinson, R.G.; Huber, H.E.; Jones, R.E.; Zhao, Z.; Duggan, M.E.; **Lindsley, C.W.** 'Tumor cell sensitization to apoptotic stimuli by selective inhibition of specific Akt/PKB family members' Anti-Cancer Drug Discovery and Development, 6th Annual Summit, Philadelphia, PA July 21-23, 2004.

15. Leister, W.H.; **Lindsley, C.W.** 'Complete high throughput analytical support for drug discovery: from customization of a preparative liquid chromatograph/mass spectrometer to plating samples for screening' World Pharmaceutical Congress - Hit-to-Lead: Streamling Lead Generation to Enhance Downstream Success, Philadelphia, PA May 18-19, 2004.

14. **Lindsley, C.W.** 'The challenges of establishing an effective lead discovery and development group' World Pharmaceutical Congress - Hit-to-Lead: Streamling Lead Generation to Enhance Downstream Success, Philadelphia, PA May 18-19, 2004 (invited speaker).

13. Duggan, M.E.; **Lindsley, C.W.**; Leister, W.H.; Strauss, K.A.; Wang, Y.; Wisnoski, D.D.; Zhao, Z. 'Application of enabling technologies to expedite drug discovery' Advances in Synthetic, Combinatorial and Medicinal Chemistry International Symposium, Moscow, Russia May 5-8, 2004.

12. **Lindsley, C.W.** 'Technology enhanced medicinal chemistry' CHI's Molecular Medicine Triconference: Mastering Medicinal Chemistry, San Francisco, CA March 26, 2004 (invited speaker).

11. **Lindsley, C.W.** 'Target and diversity-oriented organic synthesis employing microwave technology' 2nd International Microwaves in Chemistry Conference, Orlando, FL, March 5, 2004 (invited speaker).

10. Williams, D.L., O'Brien, J. A., Lemaire, W., Wittmann, M., Chen, T., Chang, R.S.L., Jacobson, M.A., Ha, S.N., Wisnoski, D.D., **Lindsley, C.W.**, Sur, C., Duggan, M.E., Pettibone, D.J., Conn, P.J. 'Actions of a novel allosteric potentiator of mGluR5 in recombinant and native systems' Society for Neuroscience, New Orleans, LA, November 8-12, 2003.

9. **Lindsley, C.W.** 'Methodology and tools to expedite the synthesis and purification of analog libraries' 35th ACS Central Regional Meeting, Pittsburgh, PA, October 22, 2003 (invited speaker).

8. **Lindsley, C.W.** 'Microwave-assisted organic synthesis: A powerful approach for small molecule construction and the expedient development of new materials' Mid-Atlantic Fall Symposium on Microwave-Assisted Organic Synthesis, Iselin, NJ, October 16, 2003 (invited speaker).

7. **Lindsley, C.W.** 'Technology enhanced medicinal chemistry – practical tools to accelerate lead discovery and development' Presented at Meeting the Challenges of Modern Medicinal Chemistry East Brunswick, NJ, October 2, 2003 (invited speaker).

6. **Lindsley, C.W.** 'Microwave-mediated synthesis: A powerful approach for small molecule construction and the expedient development of new materials' Mid-Atlantic Symposium on Microwave-Assisted Organic Synthesis, King of Prussia, PA, June 19, 2003 (invited speaker).

5. Williams, D.L. Jr.; O'Brien, J.A; Lemaire, W. Chen, T.B. Chang, R.S.L.; Jacobson, M.A., Ha, S.N.; Wisnoski, D. D.; **Lindsley, C. W.**; Sur, C.; Duggan, M.E.; Pettibone, D.J.; Conn, P. J. 'Difference in mGluR5 interaction between positive allosteric modulators from two structural classes' New York Academy of Sciences Meeting on Glutamate and Disorders of Cognition and Motivation, New Haven CT, 13-15 April 2003.

4. **Lindsley, C.W.** 'Fluorous technology for solution phase parallel synthesis' University of Pittsburgh, Departmental Seminar, Pittsburgh, PA, September 17, 2002 (invited speaker).

3. **Lindsley, C. W.** 'West Point's Technology Enabled Synthesis (TES) group: A targeted library approach to chemical lead development for nascent programs' Merck Chemistry Council Medicinal Chemistry Conference, La Sapiniere Resort, Val David, Quebec, Canada, June 15-19, 2002.

2. **Lindsley, C. W.** 'Biomimetic solid-phase synthesis of benzoxanthenone unnatural products', University of California, Santa Barbara, Departmental Seminar, Santa Barbara, CA, November 17, 1998 (invited speaker).

1. **Lindsley, C. W.** 'Novel bi-directional organometallic linchpins for all-E polyene synthesis', Chemistry Alumni Research Symposium (CARS), California State University, Chico, Chico, CA 1997.

References

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EXHIBIT B

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

WYETH LLC, WYETH PHARMACEUTICALS LLC, PF PRISM C.V., PFIZER PHARMACEUTICALS LLC, and PFIZER PFE IRELAND PHARMACEUTICALS HOLDING 1 B.V. Plaintiffs, v. ALEMBIC PHARMACEUTICALS, LTD., ALEMBIC PHARMACEUTICALS, INC. , SUN PHARMACEUTICAL INDUSTRIES LIMITED and SUN PHARMACEUTICAL INDUSTRIES, INC., Defendants.	)	C.A. No. 16-1305 (RGA) CONSOLIDATED **PUBLIC VERSION**

OPENING EXPERT REPORT OF CRAIG W. LINDSLEY, PH.D.

I. INTRODUCTION

1. I, Craig W. Lindsley, Ph.D., submit this expert report on behalf of Defendants Alembic Pharmaceuticals, Ltd., Alembic Pharmaceuticals, Inc., Sun Pharmaceuticals Industries Limited and Sun Pharmaceutical Industries, Inc. ("Defendants") in the above-captioned litigation brought by Wyeth LLC, Wyeth Pharmaceuticals Inc., PF Prism C.V., Pfizer Pharmaceuticals LLC, and Pfizer PFE Ireland Pharmaceuticals Holding 1 B.V. ("Plaintiffs").

2. In particular, I have been asked to provide a statement of my opinions based on my experience, education, training, knowledge of the literature, and materials reviewed, relating to U.S. Patent Nos. 7,417,148 ("the '148 patent") and 7,919,625 ("the '625 patent"), and. 7,767,678 ("the '678 patent"). Specifically, I have been asked to set forth technical opinions which I have been informed pertain to the validity of Claim 7 of the '148 patent,,Claim 1 of the '625 patent,[2] and Claim 12 of the '678 patent (collectively, "the Asserted Claims").

3. In addition, if asked, I may respond to the opinions and testimony of Plaintiffs' witnesses regarding issues within my area of expertise.

4. In forming my opinions and preparing this report, I reviewed and considered the materials cited in this report and the materials listed in Exhibit A to this report. I have also relied upon my knowledge, education, and training as described below and in my *curriculum vitae*, attached to this report as Exhibit B.

II. QUALIFICATIONS AND EXPERIENCE

5. I am currently one of only five University Professors at Vanderbilt, with tenure across the School of Medicine and the School of Arts and Sciences. I am also the William K.

[2] Claim 1 of the '625 patent is only asserted against the Sun defendants, not the Alembic defendants.

Warren, Jr. Chair in Medicine. At Vanderbilt, I am engaged in drug discovery, and have licensed fifteen projects to pharmaceutical partners.

6. I received my Ph.D. in Chemistry in 1996 from the University of California, Santa Barbara. Thereafter, I worked in the pharmaceutical industry as a medicinal chemist during the 1999-2006 time period in both oncology and neuroscience, during which I developed six drug candidates. At Parke-Davis, I worked on oncology programs directed at serine/threonine kinase proteins, and the preparation of new rasta resins to expedite compound synthesis. I then moved to Eli Lilly, and worked on a number of CNS programs targeting agonists and antagonists of G-protein coupled receptors ("GPCRs"). I was then recruited to Merck to lead a new effort in their medicinal chemistry department.

7. While at Merck, I worked on a number of kinase programs, and I became very familiar with chronic myelogenous leukemia ("CML") and kinase inhibitors (both ATP-competitive and allosteric). In particular, I developed the first allosteric Akt kinase inhibitors that enabled isoform specificity between Akt1, Akt2 and Akt3, and delivered key tool compounds as well as MK-2206. I also worked on IGF-1R, a tyrosine receptor kinase, and dealt with selectivity challenges of the highly homologous insulin receptor (IR) and the IGF-1R/IR heterodimer, and other kinase programs, such as Chk-1. Also while at Merck, I co-developed the field of GPCR allosteric modulators, delivering the first PAMs of M_1 and $mGlu_5$, showing unprecedented selectivity and critical target validation.

8. Moreover, from my time at three different pharmaceutical companies (and having participated in the filing of patent applications at all three, including dozens at Merck), I understand how timing and execution of invention disclosures and patent filings are handled in the pharmaceutical industry. It was the industry standard during my time, from 1999 to 2006, to

file patent applications early to ensure ownership of new chemical matter and methods of treatment. The general rule was that there could be no public disclosure of compounds or new pharmacological concepts in poster, oral or manuscript form, unless a patent application had been filed prior to disclosure. Every drug development program included a representative from the patent department, and we routinely held meetings to discuss the IP landscape and decide the content and timing of new applications; any disclosure – abstract, manuscript, slides, etc. – were sent to the project-assigned attorney for approval prior to any disclosure. At all three organizations, scientists were required to have completed lab notebook pages counter-signed and witnessed within 30 days of closing out an experiment, as the countersigned date was considered the date of conception for patent application purposes.

9. At all three companies, we would typically have 18 to 24 months from initiation of an oncology project to declaring a preclinical development candidate. The clock was started when we found a "hit"—a small molecule with favorable activity as measured through a predetermined screening assay or through reviewing the literature. We had hard milestones and deliverables. We had to move through hit-to-lead and initiate full lead optimization within 6 months. This involved a series of tests to determine tractable structure-activity relationships ("SAR"), robust chemistry, strong *in vitro* data (biochemical and cellular) and good rodent pharmacokinetics ("PK"). We also conducted patent searches to confirm we were in a chemical space with freedom to operate. Only after all this was done would we begin drafting patent applications. During this time, there would be no external disclosures of any kind related to the project. We would always file the patent application in early lead optimization ("LO"), as we had 12 months to add new examples, and the project would deliver a candidate or be terminated by that time. In LO, the team received more resources, and iterative med chem, biochemistry,

drug metabolism and pharmacokinetics ("DMPK") and *in vivo* efficacy studies accelerated, such that typically 2,000 or more compounds were synthesized and evaluated en route to candidate selection. As we narrowed the field of potential drug candidates to one (with low predicted efficacious human plasma levels), we would file a second provisional application to claim the particular key compound. Late stage multi-species *in vitro* and *in vivo* PK studies would be completed, along with tumor xenograft studies, *in vitro*/*in vivo* toxicology studies, and dose escalation studies with various formulations of the lead drug candidate. A 'package' would be presented to management for approval, and if approved, we would initiate studies to enable an investigational new drug ("IND") application. Based on a variety of factors, a back-up program may or may not be launched for the target. If not, the team was reassigned to another cancer program, and the entire process began again.

10. After Merck, I joined Vanderbilt in 2006 as an Associate Professor and Director of Medicinal Chemistry and Drug Metabolism and Pharmacokinetics ("DMPK") for the Vanderbilt Center for Neuroscience Drug Discovery ("VCNDD"). I was quickly promoted to Full Professor, and in 2018, University Professor. During my 13 years thus far at Vanderbilt, I have received numerous awards for excellence in medicinal chemistry/drug discovery, served as founding Editor-in-Chief of *ACS Chemical Neuroscience*, been named one of the World's Most Influential Minds, and routinely appear on the most cited researcher lists. I also follow the same guidelines at Vanderbilt that I followed while in industry for disclosures, patent applications, and record keeping.

11. I have published over 400 manuscripts, and am an inventor on 91 issued US patents and over 200 published patent applications. Through my involvement in obtaining these

patents I have developed an understanding of how the timing and execution of invention disclosures and patent filings are handled in the pharmaceutical industry.

12. Other accomplishments, awards, and professional memberships are noted in my *curriculum vitae*, which is attached as Exhibit B.

13. My areas of expertise include drug discovery and development, particularly in the field of oncology and with various kinase inhibitors, including both serine-threonine kinase inhibitors and tyrosine kinase inhibitors, transporters, ion channels and GPCRs. I have been working on developing tyrosine kinase inhibitors for the treatment of cancer and some fibrotic diseases for over 20 years.

III. SUMMARY OF OPINIONS

14. My opinions, which are set forth in detail below, are as follows:

- Claim 1 of the ’625 patent is anticipated by the prior art.
- Claim 7 of the ’148 patent and Claim 1 of the ’625 patent would have been obvious to a person of ordinary skill in the art as of the date of the alleged invention.[3] In reaching this opinion, I have considered the secondary considerations identified by Plaintiffs as supporting nonobviousness.
- Claim 7 of the ’148 patent, Claim 1 of the ’625 patent, and Claim 12 of the ’678 patent are not enabled;
- Claim 7 of the ’148 patent, Claim 1 of the ’625 patent, and Claim 12 of the ’678 patent lack a sufficient written description;

[3] As discussed below, I understand that Plaintiffs have alleged that the claimed invention was conceived by May 20, 2002, and the named inventors worked diligently to reduce the invention to practice beginning in November 2002. I further understand that the earliest claimed priority date of the ’148 and ’625 patents is November 6, 2003. These claims would have been obvious as of either November 6, 2002 or November 6, 2003.

became aware that other Src inhibitors could inhibit Abl, Wyeth also tested its Src inhibitors to see if they could also inhibit Abl).

74. The challenge, at that time, was not only to develop Src inhibitors capable of inhibiting cancer growth, but identify those that are also stable *in vivo* and bioavailable. Irby 2000 at 5640. By 2001, bosutinib was identified as such a Src inhibitor. *See, e.g.,* Boschelli 2001 at 3970 (determining, through a xenograft study, that compound 31a (bosutinib) was sufficiently bioavailable to inhibit the growth of Src-transformed fibroblasts).

D. Availability of § 102(a) Prior Art

75. I understand that references that were publicly disclosed after November 6, 2002, but before November 6, 2003, fall into a category of prior art referred to as § 102(a) prior art with respect to the ’148 and ’625 patents. It is also my understanding that § 102(a) references can be disqualified as prior art if Plaintiffs can establish a date of invention that predates the publication of the § 102(a) reference.

76. It is my understanding, however, that for Plaintiffs to assert an earlier date of invention, Plaintiffs must show that the named inventors not only conceived of the invention prior to the publication of the § 102(a) reference, but that the named inventors diligently worked to reduce the invention to practice from at least just prior to the date of the prior art reference. Because the subject matter claimed by the ’148 and ’625 patents was not reduced to practice prior to the filing of the priority application on November 6, 2003 (*see, e.g.*, PFE-BO801683588 at 3590, indicating that Phase I/II trials for bosutinib to treat CML did not begin until December 2005), I understand that the date of filing of the priority application is considered a date of “constructive” reduction to practice. Therefore, I understand that for Plaintiffs to challenge a given § 102(a) reference as prior art, Plaintiffs must show conception and diligence in reducing the invention to practice from at least the date of that reference (November 16, 2002 to antedate

the Boschelli 2002 reference or January 15, 2003 to antedate the Golas 2003 reference) to November 6, 2003.

77. I have reviewed the evidence that Plaintiffs cite in support of their assertion of diligence, and it is my opinion that the named inventors did not diligently work to reduce the invention to practice between either November 16, 2002 and November 6, 2003 or January 15, 2003 and November 6, 2003.

78. Plaintiffs have asserted a conception date at least as early as May 20, 2002. *See* Plaintiffs' Supplemental Objections and Responses to Defendants' First Set of Interrogatories dated November 9, 2018, at Supplemental Response to Interrogatory No. 1. Plaintiffs further assert that "[a]t least throughout the period from shortly before the publication of the Donato 2002 reference on November 16, 2002, through the filing of U.S. Provisional Application 60/517,819 on November 6, 2003, the named inventors and their colleagues who were involved in the development of bosutinib worked diligently to reduce the inventions of the '148 and '625 patents to practice." *See* Plaintiffs' Second Supplemental Objections and Response to Defendants' Interrogatory No. 1, dated January 11, 2019, at p. 3.

79. All of the data that was incorporated into the specification of the '148 and '625 patents was obtained before May 20, 2002, as indicated by a draft for a Cancer Research article that eventually published January 15, 2003 as the Golas 2003 reference. *See, e.g.,* PFE-BOS01772244 and PFE-BOS01772245. The May 2002 draft of the Cancer Research article identifies the three named inventors of the '148 and '625 patents among its authors: Jennifer Weber (maiden name of Jennifer Golas), Kim Arndt, and Frank Boschelli. PFE-BOS01772245. This draft discloses that SKI-606, or bosutinib, is not only a Src inhibitor, but "is shown here to be a potent antiproliferative and pro-apoptotic agent against chronic myelogenous leukemia cells

in culture, at least in part because SKI-606 is also a potent Abl kinase inhibitor." *Id*. at 2258. The last paragraph of the May 2002 draft article states the following: "Simultaneous inhibition of two signal transduction targets important in CML could offer significant therapeutic advantages for patients refractory to STI-571 treatment." *Id*. at 2260. Thus, at least as early as May 2002, the named inventors of the '148 and '625 patents appreciated that bosutinib, which simultaneously inhibits Src and Bcr-Abl, two of the signal transduction targets important in CML, could offer significant therapeutic advantages for patients refrractory to Gleevec.

80. However, the last paragraph of the May 2002 draft article also states: "We caution that to date, the toxicological properties of SKI-606 have not been examined." *Id*. at 2260. Thus, as of May 2002, toxicological studies of bosutinib necessary to determine a therapeutically effective dose had not yet been performed. As a Wyeth employee testified, rat and dog oral maximum-tolerated-dose ("MTD") studies would be the first studies performed to develop bosutinib for an oral oncology indication, such as CML. Clarke Dep. Tr. 36:11-15.[5]

81. However, these oral MTD studies did not begin until long after May 20, 2002. Instead, while oral toxicology studies for bosutinib were planned for November 2002, they were inexplicably delayed until January 2003. *Compare* PFE-BOS01593573 ("The rat and dog oral MTD studies are tentatively scheduled for late November") with PFE- B0S01593603 ("The rat and dog oral MTD studies are tentatively scheduled to begin dosing in mid January"). In fact, toxicology studies for bosutinib did not begin until at least January 28, 2003. *See, e.g.*, PFE-BOS01593199 (January 15, 2003 Src meeting minutes stating that "[t]he start date for the rat oral

[5] While I understand that rat and dog IV MTD studies were being performed, these IV toxicity studies were done for the stroke indication, which would not apply to an oncology indication such as CML.

MTD study is January 28"); *see also* PFE-BOS01588107 (disclosing that "[t]he dog oral MTD study date is scheduled to begin on March 4th [2003]")

82. Thus, after May 20, 2002, there is no evidence of work done to pursue even toxicology studies in rats and mice until after the publication of the Golas 2003 article on January 15, 2003—on January 28, 2003. Plaintiffs have not produced any evidence to show that there was any work done to reduce the inventions of the '148 and '625 patents to practice prior to the publication of the Boschelli 2002 reference on November 16, 2002 or the Golas 2003 article on January 15, 2003. The months of inactivity relating to development of bosutinib for a CML indication show that the named inventors were not diligent in reducing to practice the subject matter claimed by claim 7 of the '148 patent and claim 1 of the '625 patent.

83. I reserve the right to supplement my opinions on diligence in response to any additional evidence provided by Plaintiffs in a responsive expert report.

E. Scope And Content Of The Prior Art Prior to November 6, 2002

84. Without intending to be limiting, I provide below descriptions of disclosures and teachings of prior art references that relate to the subject matter of the '148 and '625 patents. These disclosures and teachings are representative of the general knowledge of a POSA and the scope of the prior art as of November 6, 2002, one year prior to the earliest priority date of the'148 and '625 patents, which I understand to be the critical date before which any patent or printed publication may be considered § 102(b) prior art to the '148 and '625 patents. It is my understanding that a patentee cannot overcome a reference that is considered § 102(b) prior art reference by claiming an earlier date of invention.

1. Danhauser-Riedl et al., *Activation of Src Kinases p53/56lyn and p59hck by p210bcr/abl in Myeloid Cells,* Cancer Research 56:3589 (1996) ("Danhauser 1996")

Respectfully submitted,

Dated: April 24, 2019

Craig W. Lindsley

EXHIBIT C

PUBLIC VERSION

WYETH LLC, et al vs.
ALEMBIC PHARMACEUTICALS, LTD., et al

CRAIG W. LINDSLEY

August 9, 2019

Original File 280367.txt

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that plaintiffs cite in support of their assertion of diligence, and it is my opinion that the named inventors did not work -- did not diligently work to reduce the invention of practice between either November 16, 2002, and November 6, 2003, or January 15, 2003, and November 6, 2003."

What -- what expertise do you have in what constitutes diligence to reduce an invention of practice?

A. Well, it -- you know, so both at Merck -- I would say not so much, but the time at Vanderbilt, we work with pharmaceutical companies. They license our programs. We co -- we codevelop them with them. And one of the things we have in all of our contracts are very strong diligence language on timelines for development.

We can't get companies to agree to maintenance fees, but we always make them agree to timeline-based diligence, so that assets don't sit. We don't want things to be parked at the IND-enabling study stage; we don't want to park something at Phase 1. So they had defined times to move things along.

But then internally at Merck, I mean, I wouldn't necessarily call it "diligence,"

necessarily, as -- as that defined term, but when we have a program, we had defined terms in which to get through certain milestones that was handed down by the company, the head of the different divisions.

And so in terms of the oncology clinicians, the clinical enterprise, they provided the development team defined timelines, which you can consider diligence, by which this has to be done by this timeline; you know, everything was 1Q here, 2Q here. You have to be here, you have to be here, you have to be here.

So there were defined milestones, which you could just assume would be diligence. But I've done a lot of diligence writing to make sure partners don't park assets at various stages.

Q. During your Ph.D. program, did you take any classes on diligence to reduction of practice?

A. That was not part of the Ph.D. program.

Q. Have you ever taught a class on diligence to reduction of practice?

A. No, I have not.

Q. How many articles have you published?

A. I have not published any articles on diligence.

Q. But how many articles have you published?
A. Oh. Well over 500.
Q. And none of those relate to diligence?
A. No. They're all scientific articles.
Q. Are you aware of any peer-review journal in which an article about diligence to reduction of practice appears?
A. I am not.
Q. If you turn to page 57, there's a -- Section 9 says, "Claim 1 of the '625 patent is invalid as anticipated by Boschelli 2001."
Do you see that?
A. Yes, I do.
Q. And then there is several paragraphs in -- in that section. You just want to maybe just read those, just to put -- put context -- I'm only going to ask you questions about 162, but for context, if you can just read the other ones -- I'm sorry, 163.
A. Okay.
Q. If you go to paragraph 163. You state, "Furthermore, assuming that CML-inhibiting amount means therapeutically effective, the dosing regimen will determine whether a given pharmaceutical composition is CML-inhibiting or therapeutically effective."

And then it says, "As explained above, no single dose can provide a therapeutically effective amount. However, it is possible that 3 milligram bosutinib administered to a human patient 167 times a day for prescribed number of days could cure or ameliorate the symptoms of CML, and thus be a therapeutically effective or CML-inhibiting amount."

By November 6, 2002, could a scientist working in the field have determined that 167 -- administering 3 milligrams of bosutinib 167 times per day would be a therapeutically effective amount --

MR. GRAVELINE: Objection to the form.

Q. -- for treating CML?

MR. GRAVELINE: I'm sorry. Objection to the form.

A. Could you rephrase that, or say that question again, please?

Q. Sure. If I used the phrase "person of ordinary skill in the art," do you know what I mean?

A. Mm-hmm.

Q. Or POSA?